IN THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (previously presented) A method of treating a mammalian subject to inhibit restenosis of a blood vessel, comprising the step of:

administering to a mammalian subject in need of treatment to inhibit restenosis of a blood vessel a composition comprising a polynucleotide,

wherein said composition is administered locally at the site in need of treatment to inhibit restenosis,

wherein said polynucleotide comprises a nucleotide sequence that encodes a vascular endothelial growth factor C (VEGF-C) polypeptide operatively linked to a promoter to promote expression of the VEGF-C polypeptide in cells of the blood vessel, and

wherein expression of said VEGF-C polypeptide in said blood vessel cells inhibits restenosis of said blood vessel.

2. (original) A method according to claim 1 wherein said mammalian subject is human.

3. (original) A method according to claim 2 wherein said VEGF-C polypeptide comprises a mammalian VEGF-C.

4. (original) A method according to claim 2 wherein said VEGF-C polypeptide comprises a human VEGF-C.

5. (original) A method according to claim 2 wherein said VEGF-C polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 2, said continuous portion having, as its amino terminus, an amino acid selected from the group consisting of positions 30-131 of SEQ ID NO: 2, and having, as its carboxyl terminus, an amino acid selected from the group consisting of positions 211 to 419 of SEQ ID NO: 2.

6. (original) A method according to claim 5 wherein said polynucleotide further comprises a nucleotide sequence encoding a secretory signal peptide, and wherein the sequence encoding the secretory signal peptide is connected in-frame with the sequence that encodes the VEGF-C polypeptide.

7. (original) A method according to claim 6 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 228-419 of SEQ ID NO: 2.

8. (original) A method according to claim 7 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 32-102 of SEQ ID NO: 2.

9. (canceled)

10. (previously presented) A method according to claim 1 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-C polypeptide.

11. (original) A method according to claim 2 wherein the composition further comprises a pharmaceutically acceptable carrier.

12. (original) A method according to claim 2 wherein the composition comprises a gene therapy vector, said gene therapy vector comprising said polynucleotide.

13. (previously presented) A method according to claim 12 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide operably connected to the promoter and flanked by adenoviral polynucleotide sequences.

14. (previously presented) A method according to claim 2 wherein said administering comprises at least one intravascular injection of said composition.

15. (previously presented) A method according to claim 2 wherein said administering comprises a catheter-mediated transfer of said composition into a blood vessel of the mammalian subject.

16. (original) A method according to claim 15 wherein said catheter-mediated gene transfer comprises introducing a catheter into a coronary artery of the mammalian subject, and releasing the composition into the coronary artery.

17. (original) A method according to claim 2 wherein said administering is conducted in said human concurrently with a percutaneous transluminal coronary angioplasty.

18. (previously presented) A treatment to inhibit restenosis of a blood vessel in a human, comprising delivering a replication-deficient adenovirus vector to the vessel, said vector comprising a polynucleotide encoding a VEGF-C polypeptide, and further comprising a promoter sequence to promote expression of the VEGF-C polypeptide in cells of the blood vessel, wherein expression of said VEGF-C polypeptide in said blood vessel cells inhibits restenosis of the blood vessel.

19. (canceled)

20. (canceled)

21. (withdrawn) A method of treating a mammalian subject to inhibit restenosis of a blood vessel, comprising the step of:

administering to a mammalian subject in need of treatment to inhibit restenosis of a blood vessel a composition locally at a site in need of treatment to inhibit restenosis, said composition comprising a polynucleotide comprising a nucleotide sequence that encodes a vascular endothelial growth factor D (VEGF-D) polypeptide operatively linked to a promoter to promote expression of the VEGF-D polypeptide in cells of the blood vessel, wherein expression of said VEGF-D polypeptide in said blood vessel cells inhibits restenosis of said blood vessel.

22. (previously presented) An improvement in a medical device designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel, said improvement comprising integrating into the device a composition effective to prevent restenosis, said composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C in cells of blood vessels, and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D in cells of blood vessels.

23. (original) The improvement of claim 22, wherein the device is selected from the group consisting of intravascular stents, intravascular catheters, and combinations thereof.

24. (original) The improvement of claim 22, wherein the device comprises an extravascular collar.

25. (original) The improvement of claim 22, wherein the device comprises an elastomeric membrane adapted to cover a surface of an intravascular stent or catheter.

26. (previously presented) A medical device comprising an endovascular stent having an outer surface for contacting a surface of a blood vessel, and a composition on said surface, said composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels.

27. (previously presented) A medical device comprising a catheter having an outer surface for contacting a surface of a blood vessel, and a composition on said surface, said composition comprising at least one member selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels.

28. (previously presented) A medical device comprising a balloon catheter having a void for holding a therapeutic agent for delivery to the interior of a blood vessel, and a composition contained in the void, the composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels.

29. (previously presented) A kit for treating restenosis comprising a container holding at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C in cells of blood vessels and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D in cells of blood vessels; and a label attached to or packaged with the container, the label describing use of the agent for inhibition of restenosis of a blood vessel.

30. (original) A kit according to claim 29, further comprising a medical device selected from the group consisting of: intravascular stents, intravascular catheters, extravascular collars, and membranes adapted to cover a surface of an intravascular stent or catheter.

31. (previously presented) A kit according to claim 30, further comprising a carrier substance for delivery of the agent to the lumenal wall of a vessel.

32. (previously presented) A kit according to claim 31, wherein the carrier is selected from the group consisting of a hydrogel polymer and microparticle polymers.

33. (withdrawn) A method according to claim 21 wherein said mammalian subject is human.

34. (withdrawn) A method according to claim 33 wherein said VEGF-D polypeptide comprises a mammalian VEGF-D.

35. (withdrawn) A method according to claim 33 wherein said VEGF-D polypeptide comprises a human VEGF-D.

36. (withdrawn) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion consisting of positions 93-201 of SEQ ID NO: 4.

37. (withdrawn) A method according to claim 36 wherein said polynucleotide further comprises a nucleotide sequence encoding a secretory signal peptide, and wherein the sequence encoding the secretory signal peptide is connected in-frame with the sequence that encodes the VEGF-D polypeptide.

38. (withdrawn) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 1-92 of SEQ ID NO: 4.

39. (withdrawn) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 202-354 of SEQ ID NO: 4.

40. (withdrawn) A method according to claim 21 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-D polypeptide.

41. (withdrawn) A method according to claim 33 wherein the composition further comprises a pharmaceutically acceptable carrier.

42. (withdrawn) A method according to claim 33 wherein the composition comprises a gene therapy vector, said gene therapy vector comprising said polynucleotide.

43. (withdrawn) A method according to claim 42 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide operably connected to the promoter and flanked by adenoviral polynucleotide sequences.

44. (withdrawn) A method according to claim 33 wherein said administering comprises at least one intravascular injection of said composition.

45. (withdrawn) A method according to claim 33 wherein said administering comprises a catheter-mediated transfer of said composition into a blood vessel of the mammalian subject.

46. (withdrawn) A method according to claim 45 wherein said catheter-mediated gene transfer comprises introducing a catheter into a coronary artery of the mammalian subject, and releasing the composition into the coronary artery.

47. (withdrawn) A method according to claim 33 wherein said administering is conducted in said human concurrently with a percutaneous transluminal coronary angioplasty.

48. (withdrawn) A treatment to inhibit restenosis of a blood vessel in a human, comprising delivering a replication-deficient adenovirus vector to the vessel, said vector comprising a polynucleotide encoding a VEGF-D polypeptide, and further comprising a promoter sequence to promote expression of the VEGF-D polypeptide in cells of the blood vessel, wherein expression of said VEGF-D polypeptide in said blood vessel cells inhibits restenosis of the blood vessel.

49. (previously presented) A method of treating a mammalian subject to inhibit restenosis of a blood vessel, comprising the step of:

identifying a mammalian subject that has been or will be treated for a stenosed blood vessel; and

administering to the mammalian subject at the site of the stenosed blood vessel a composition comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence that encodes a vascular endothelial growth factor C (VEGF-C) polypeptide or a vascular endothelial growth factor D (VEGF-D) polypeptide,

wherein the polynucleotide includes a promoter sequence operably linked to the encoding sequence to promote expression of the polypeptide in cells of the blood vessel, and

wherein expression of the VEGF-C or VEGF-D polypeptide inhibits restenosis of said blood vessel.

50. (previously presented) A method according to claim 49 wherein said mammalian subject is human.

51. (previously presented) A method according to claim 49 wherein the blood vessel is a coronary artery, and the administering is performed concurrently with percutaneous transluminal coronary angioplasty to treat the stenosed blood vessel.

52. (previously presented) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a mammalian VEGF-C polypeptide.

53. (previously presented) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a human VEGF-C polypeptide.

54. (previously presented) A method according to claim 53 wherein said VEGF-C polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 2, said continuous portion having, as its amino terminus, an amino acid selected from the group consisting of positions 30-131 of SEQ ID NO: 2, and having, as its carboxyl terminus, an amino acid selected from the group consisting of positions 211 to 419 of SEQ ID NO: 2.

55. (previously presented) A method according to claim 54 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 228-419 of SEQ ID NO: 2.

56. (previously presented) A method according to claim 55 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 32-102 of SEQ ID NO: 2.

57. (previously presented) A method according to claim 49 wherein said polynucleotide further comprises a nucleotide sequence encoding a secretory signal peptide, and wherein the sequence encoding the secretory signal peptide is connected in-frame with the sequence that encodes the VEGF-C or VEGF-D polypeptide.

58. (previously presented) A method according to claim 57 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-C or VEGF-D polypeptide.

59. (withdrawn) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a mammalian VEGF-D polypeptide.

60. (withdrawn) A method according to claim 59 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion consisting of positions 93-201 of SEQ ID NO: 4.

61. (withdrawn) A method according to claim 59 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 1-92 of SEQ ID NO: 4.

62. (withdrawn) A method according to claim 59 A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 202-354 of SEQ ID NO: 4.

63. (previously presented) A method according to claim 49 wherein the composition comprises a gene therapy vector, said gene therapy vector comprising said polynucleotide.

64. (previously presented) A method according to claim 63 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide flanked by adenoviral polynucleotide sequences.

65. (previously presented) A method according to claim 49 wherein the composition further comprises a pharmaceutically acceptable carrier.

66. (previously presented) A method according to claim 49 wherein said administering comprises at least one intravascular injection of said composition at the site of the stenosed blood vessel.

67. (previously presented) A method according to claim 49 wherein said administering comprises a catheter-mediated transfer of said composition to the site of the stenosed blood vessel.

68. (previously presented) A method according to claim 49 wherein said catheter-mediated gene transfer comprises introducing a catheter into a coronary artery of the mammalian subject, and releasing the composition into the coronary artery.

69. (previously presented) A method according to claim 49 wherein said administering comprises implanting an intravascular stent in said mammalian subject at the site of the stenosed blood vessel, and wherein the stent is coated or impregnated with the composition.

70. (previously presented) An extravascular collar designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel, the collar comprising an outer wall shaped to surround the outer surface of a blood vessel, wherein the wall encloses a space containing a composition comprising a polynucleotide that comprises a nucleotide sequence encoding a VEGF-C polypeptide or a VEGF-D polypeptide, and wherein the polynucleotide further comprises a promoter to promote expression of the polypeptide in mammalian cells.

71. (previously presented) A unit dosage formulation comprising a polynucleotide that comprises a promoter for promoting expression of a polypeptide in mammalian cells operably linked to a nucleotide sequence encoding a VEGF-C polypeptide or a VEGF-D polypeptide, packaged in a container, wherein the container includes a label containing an indication to use the formulation to treat restenosis.

72. (previously presented) A unit dose formulation according to claim 71 wherein the agent is in admixture with a pharmaceutically acceptable carrier.

73. (previously presented) A method according to any one of claims 2, 4, 12, 17, 21, 35, 45, 47, 50, 53, and 59, further comprising administering to said subject an inhibitor of smooth muscle cell growth or migration.

74. (previously presented) A device according to any one of claims claim 22, 26, 27, and 28, wherein the composition further comprises an inhibitor of smooth muscle cell growth or migration.

75. (previously presented) A method according to any one of claims 1, 2, 10-17, 49-51, 57-58, and 63-69, wherein the VEGF-C polypeptide comprises a continuous portion of the amino acid sequence set forth in SEQ ID NO: 2 sufficient to bind, and stimulate phosphorylation of, at least one receptor selected from the group consisting of VEGFR-2 and VEGFR-3, in cells that express said at least one receptor.

76. (previously presented) A method according to claim 75, wherein the polypeptide comprises amino acids 131-211 of SEQ ID NO: 2.

77. (previously presented) A method according to claim 75, further comprising administering to said subject an inhibitor of smooth muscle cell growth or migration.

78. (previously presented) A method according to any one of claims 1, 2, 10-17, 49-51, 57-58, and 63-69, wherein the polynucleotide comprises a nucleotide sequence that will hybridize to a polynucleotide that is complementary to the human VEGF cDNA sequence specified in SEQ ID NO: 1 under the following exemplary stringent hybridization conditions: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM $Na•PO_4$, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes; and wherein the nucleotide sequence encodes a polypeptide that binds and stimulates at least one receptor selected from the group consisting of human VEGFR-2 and VEGFR-3.

79. (previously presented) A method according to claim 78, further comprising administering to said subject an inhibitor of smooth muscle cell growth or migration.

80. (previously presented) A treatment according to claim 18, wherein the VEGF-C polypeptide comprises a continuous portion of the amino acid sequence set forth in SEQ ID NO: 2 sufficient to bind, and stimulate phosphorylation of, at least one receptor selected from the group consisting of VEGFR-2 and VEGFR-3, in cells that express said at least one receptor.

81. (previously presented) A treatment according to claim 80, wherein the polypeptide comprises amino acids 131-211 of SEQ ID NO: 2.

82. (previously presented) A treatment according to claim 18, wherein the polynucleotide comprises a nucleotide sequence that will hybridize to a polynucleotide that is complementary to the human VEGF cDNA sequence specified in SEQ ID NO: 1 under the following exemplary stringent hybridization conditions: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM $Na•PO_4$, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes; and wherein the nucleotide sequence encodes a polypeptide that binds and stimulates at least one receptor selected from the group consisting of human VEGFR-2 and VEGFR-3.

83. (previously presented) An improvement according to any one of claims 22-25, wherein the VEGF-C polynucleotide encodes a VEGF-C polypeptide that comprises a continuous portion of the amino acid sequence set forth in SEQ ID NO: 2 sufficient to bind, and stimulate phosphorylation of, at least one receptor selected from the group consisting of VEGFR-2 and VEGFR-3, in cells that express said at least one receptor.

84. (previously presented) An improvement according to claim 83, wherein the polypeptide comprises amino acids 131-211 of SEQ ID NO: 2.

85. (previously presented) An improvement according to any one of claims 22-25, wherein the VEGF-C polynucleotide comprises a nucleotide sequence that will hybridize to a polynucleotide that is complementary to the human VEGF cDNA sequence specified in SEQ ID NO: 1 under the following exemplary stringent hybridization conditions: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM $Na•PO_4$, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes; and wherein the nucleotide sequence encodes a polypeptide that binds and stimulates at least one receptor selected from the group consisting of human VEGFR-2 and VEGFR-3.

86. (previously presented) A medical device according to any one of claims 26-28, wherein the VEGF-C polynucleotide encodes a VEGF-C polypeptide that comprises a continuous portion of the amino acid sequence set forth in SEQ ID NO: 2 sufficient to bind, and stimulate phosphorylation of, at least one receptor selected from the group consisting of VEGFR-2 and VEGFR-3, in cells that express said at least one receptor.

87. (previously presented) A medical device according to claim 86, wherein the composition further comprises an inhibitor of smooth muscle cell growth or migration.

88. (previously presented) A medical device according to claim 86, wherein the polypeptide comprises amino acids 131-211 of SEQ ID NO: 2.

89. (previously presented) A medical device according to any one of claims 26-28, wherein the VEGF-C polynucleotide comprises a nucleotide sequence that will hybridize to a polynucleotide that is complementary to the human VEGF cDNA sequence specified in SEQ ID NO: 1 under the following exemplary stringent hybridization conditions: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM $Na•PO_4$, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes; and wherein the nucleotide sequence encodes a polypeptide that binds and stimulates at least one receptor selected from the group consisting of human VEGFR-2 and VEGFR-3.

90. (previously presented) A medical device according to claim 89, wherein the composition further comprises an inhibitor of smooth muscle cell growth or migration.

91. (previously presented) A kit according to claim 29 or 30, wherein the VEGF-C polynucleotide encodes a VEGF-C polypeptide that comprises a continuous portion of the amino acid sequence set forth in SEQ ID NO: 2 sufficient to bind, and stimulate phosphorylation of, at least one receptor selected from the group consisting of VEGFR-2 and VEGFR-3, in cells that express said at least one receptor.

92. (previously presented) A kit according to claim 91, wherein the polypeptide comprises amino acids 131-211 of SEQ ID NO: 2.

93. (previously presented) A kit according to claim 91, further comprising an inhibitor of smooth muscle cell growth or migration.

94. (previously presented) A kit according toclaim 29 or 30, wherein the VEGF-C polynucleotide comprises a nucleotide sequence that will hybridize to a polynucleotide that is complementary to the human VEGF cDNA sequence specified in SEQ ID NO: 1 under the following exemplary stringent hybridization conditions: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM $Na•PO_4$, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes; and wherein the nucleotide sequence encodes a polypeptide that binds and stimulates at least one receptor selected from the group consisting of human VEGFR-2 and VEGFR-3.

95. (previously presented) An extravascular collar according to claim 70, wherein the polynucleotide encodes a VEGF-C polypeptide that comprises a continuous portion of the amino acid sequence set forth in SEQ ID NO: 2 sufficient to bind, and stimulate phosphorylation of, at least one receptor selected from the group consisting of VEGFR-2 and VEGFR-3, in cells that express said at least one receptor.

96. (previously presented) An extravascular collar according to claim 95, wherein the polypeptide comprises amino acids 131-211 of SEQ ID NO: 2.

97. (previously presented) An extravascular collar according to claim 70, wherein the polynucleotide comprises a nucleotide sequence that will hybridize to a polynucleotide that is complementary to the human VEGF cDNA sequence specified in SEQ ID NO: 1 under the following exemplary stringent hybridization conditions: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM $Na•PO_4$, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes; and wherein the nucleotide sequence encodes a polypeptide that binds and stimulates at least one receptor selected from the group consisting of human VEGFR-2 and VEGFR-3.

98. (previously presented) A unit dosage formulation according to claim 71, wherein the nucleotide sequence encodes a VEGF-C polypeptide that comprises a continuous portion of the amino acid sequence set forth in SEQ ID NO: 2 sufficient to bind, and stimulate phosphorylation of, at least one receptor selected from the group consisting of VEGFR-2 and VEGFR-3, in cells that express said at least one receptor.

99. (previously presented) A unit dosage formulation according to claim 97, wherein the polypeptide comprises amino acids 131-211 of SEQ ID NO: 2.

100. (previously presented) A unit dosage formulation according to claim 71, wherein the nucleotide sequence hybridizes to a polynucleotide that is complementary to the human VEGF cDNA sequence specified in SEQ ID NO: 1 under the following exemplary stringent hybridization conditions: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM $Na•PO_4$, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes; and wherein the nucleotide sequence encodes a polypeptide that binds and stimulates at least one receptor selected from the group consisting of human VEGFR-2 and VEGFR-3.